REMARKS

By the foregoing amendments, claim 2 has been amended and claim 3 has been canceled without prejudice as to the subject matter contained therein. Support for the amendment to claim 2 can be found in the specification at page 54, line 31 to page 55, line 12; page 57, lines 1-9 and 20-29; page 62, line 32 to page 63, line 7; to page 65, line 35 to page 69, line 33; and in Examples 1-3.

Priority Claim and Effective Filing Date

The paragraph claiming priority is allegedly confusing. As suggested by the Examiner, a direct line of continuing applications has been set forth by the foregoing amendments to the specification.

The Examiner contends that the effective filing date of the claims is February 13, 2002, the filing date of the amendment in which the claims were presented, because the subject matter is allegedly not supported by the subject specification or apparently any predecessor applications. Applicants submit that the effective filing date of the subject amended claims is at least as early as the filing date of predecessor USSN 07/714,131, June 10, 1991, because the amended claims are fully supported by the subject specification which is identical to that of USSN 07/714,131. The written description that supports the amended claims is set forth in detail below in response to the Section 112, first paragraph, rejection.

Applicants also submit that the subject claims are enabled by the subject specification and its predecessors at least back to USSN 07/714,131, which is identical to the subject application. The subject application not only describes the claimed invention, as is discussed below, but also exemplifies it in Examples 1-3, where it is shown that the binding site in a region of DNA or RNA for a binding protein can be determined by using a ligand that inhibits binding of the binding protein to the DNA or RNA. The inhibitory ligand, by its nucleotide sequence or secondary or tertiary structure, can yield information about the binding site in the RNA or DNA. It is therefore respectfully submitted that the subject claims are fully described and enabled by USSN 07/714,131, and therefore have an effective filing date of June 10, 1991.

The Rejections under 35 USC § 112, First Paragraph

Claims 2-8 stand rejected under Section 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The claimed method is directed to identifying the binding site on an RNA/DNA region at which the binding protein binds, by mixing the binding protein with the RNA/DNA region and ligand and determining whether the ligand inhibits binding of the binding protein to the RNA/DNA region. The sequence or structure of ligands which are found to be inhibitory assist in the identification of the binding site on the RNA/DNA.

The Examiner asserts that the passages cited by the Applicants in support of claim 2 do not support the recitation that identification of the binding site can be accomplished by competition assays between binding region DNA or RNA and the ligand, for the binding protein. The Examiner also points out that the specification refers only to competition assays in which the binding protein's active site is assessed, not the binding site.

Applicants respectfully direct the Examiner's attention to page 62, line 32 to page 63, line 8, which describes ligands that inhibit the function of binding proteins to bind to nucleic acids:

> The methods of the present invention are useful for obtaining nucleic acids which will inhibit function of a target protein, and are particularly useful for obtaining nucleic acids [ligands] which inhibit the function of proteins whose function involves binding to nucleic acids . . ..

A competitive assay involving binding protein and inhibitory ligand, may be carried out by methods known in the art, such as by determining whether a labeled ligand does or does not bind to a binding protein in a mixture of ligand, binding protein and RNA/DNA region. Such method can be carried out via column chromatography or other known methods. Additionally, binding of binding protein to the RNA/DNA region can

be assessed by determining whether the complex of binding protein and RNA/DNA region exhibits it's characteristic catalytic function. Measuring catalytic function, in some cases, can reflect whether the binding protein has or has not been inhibited by the ligand from binding the RNA/DNA region.

The Applicants also direct the Examiner's attention to page 65, line 35 to page 69, line 33, wherein the experiment of Example 1 is described. The gp43 protein was known to bind to its own mRNA at its translational operator and suppress translation thereof. The translational operator was known to be a hairpin loop structure in which mutations in the double stranded section could be detrimental to gp43 binding. SELEX was carried out using a candidate mixture of RNA sequences containing the known operator sequence with a randomized loop section. After multiple rounds of selection and amplification, two major ligand solutions were found. One was the wild type loop sequence and the other had an affinity that was substantially equivalent to that of wild type. All of the selected ligands were found to act as inhibitors of gp43 polymerase activity, presumably meaning that all of the ligands bound gp43 with a Kd that would be sufficient to reduce binding of gp43 to its message.

This example illustrates how a ligand that binds to the binding site of a DNA/RNA binding protein can be useful in identifying the binding site of the DNA/RNA, because the inhibitory ligand's sequence can be similar to that of the binding site on the wild type mRNA.

In Example 2, ligands to the HIV RT heterodimer are selected. The RT heterodimer was known to interact with $tRNA^{Lys3}$. For candidate mixtures, two populations were used: a population of completely random 32-mers with flanking constant regions; and a population of random 32-mers with the same flanking constant regions plus a constant 5' region having the known $tRNA^{Lys3}$ anticodon loop and stem. After multiple SELEX experiments, a number of pseudoknots were determined to have a high affinity for HIV RT. The highest affinity ligand, clone 1.1, was found to inhibit RT activity as compared to the starting candidate population (page 81). Thus, the 1.1 clone to RT was concluded to either block or directly interact with the catalytic site of RT.

This example illustrates how a ligand that binds to a binding site of an RNA binding protein can have sequence and/or structure that is informative about the binding

site on the RNA (in this case, tRNA). In this case, the inhibitory ligand also happened to interfere with the active site of the binding protein.

Example 3 describes nucleic acid ligands to bacteriophage R17 coat protein. The binding of the coat protein to its RNA binding site represses translation of the R17 replicase coding region. The selected ligands have a sequence that has similarity to the natural binding site on the R17 genome.

The Examiner notes that Applicants should amend the claim in such a manner that meets utility standards of the Patent Act, and that a method whose only object is to further research is not patentable. Applicants have amended the claim, but the utility remains the same. The practical utility is that of identifying RNA/DNA binding sites to which the binding protein binds, thereby permitting the delivery to that site of other components which may be naturally or recombinantly appended to the binding protein. Further, isolated RNA/DNA binding sites can be used in heterologous constructs to selectively alter gene expression (page 54, line 31 to page 55, line 12).

The Rejection under 35 USC § 112, Second Paragraph

Claims 2-8 stand rejected under Section 112, second paragraph, as allegedly indefinite.

(A) Claims 2-8 are allegedly confusing because the method steps do not lead to a clear identification of a binding site in the RNA or DNA. By the foregoing amendments, it is believed that it is now clear that the binding site is located in the RNA or DNA, not the binding protein. Support for the concept of binding sites in DNA or RNA can be found at page 57, lines 4-9.

(B) The claims are allegedly unclear in the recitations of "region of a DNA or RNA" because "region" is a term that is not defined in the claims or specification relative to "binding site." By the foregoing amendments to claim 2, it is believed that it has now been made clear that a "binding site" is the sequence within the "DNA or RNA region" to which the binding protein binds.

(C) Claim 2(c) is rejected for lack of antecedent basis for "added nucleic acid ligand" and step (b) is rejected for lack of antecedent basis for "contacting." By the foregoing amendment step (b) has been amended to recite "adding" instead of

"contacting," thereby providing antecedent basis for "added nucleic acid ligand" in step (c).

(D) Claim 2(c) is rejected for lack of antecedent basis for "assists in identifying" and "regulatory region." By the foregoing amendment, "regulatory" has been deleted from step (c). Regarding "assists in identifying", it is respectfully submitted that this does not require antecedent basis because it's recitation in step (c) is not preceded by "the" or "said." Support for the "assists in identifying" can be found in the specification at page 54, lines 31-34.

(E) Claim 3's recitation of "having a similar structure" is rejected as allegedly confusing as to whether it means primary, secondary or tertiary structure, and how such structure could relate to "identification of the regulatory region." Note that claim 3 has been canceled but "similar structure" has been inserted in claim 2. Structures of nucleic acids were known in the art (at the effective filing date of this application) to include primary, secondary and tertiary structures. Primary structure was known to mean nucleotide sequence (see enclosed Henderson's Dictionary of Biological Terms, E. Lawrence (ed.), 10^{th} ed., 1989). Also, page 7, lines 3-10, of the specification refers to secondary and tertiary structures of RNA and DNA.

The primary, secondary or tertiary structure of the inhibitory ligand can assist in the identification of the binding site in several ways. The primary structure or sequence of the ligand can have homology with the binding site in the RNA or DNA. The secondary or tertiary structure of the ligand can be similar or the same as that which is found in the binding site, even if there is little sequence homology. Example 2 illustrates that a number of inhibitory ligands to HIV RT all having a pseudoknot structure exhibit a high affinity to the HIV RT. As discussed at page 79, line 21 to page 80, line 17, the specification discusses how inhibitory ligands can have both regions of conserved primary structure (sequence) and regions of conserved secondary or tertiary structure without conserved sequence (e.g., pseudoknots). The skilled artisan would have appreciated that this information could be used to identify homologous or structurally similar regions in the RNA or DNA to determine the location of the binding site. For these reasons, it is submitted that the sequence and/or structure of the inhibitory ligand can be useful in locating the binding site in the RNA or DNA.

The Rejections under 35 USC §§ 102(b) and/or 103(a)

Claims 2, 3 and 5-8 stand rejected under Section 102(b) as anticipated by Giordano et al., U.S. 5,859,227. As is discussed above, the Applicants submit that the effective filing date of the subject claims is June 10, 1991. Therefore, the '227 patent is not considered prior art.

Claims 2, 3, 5, 6 and 8 stand rejected under Section 102(b) as anticipated by Weissman et al., U.S. 5,861,246. Claim 4 stands rejected under 102(b) as anticipated by, or in the alternative, under Section 103(a) as obvious over the '246 patent. Because the effective filing date of the subject claims is June 10, 1991, the '246 patent is not prior art.

Withdrawal of the Section 102(b) and 103(a) rejections is respectfully requested.

Closing Remarks

It is believed that the foregoing amendments and remarks bring the subject case into condition for allowance and notification of same is respectfully requested. If the Examiner believes that a phone conference would expedite prosecution, she is invited to phone the undersigned.

Submitted herewith is a Petition for Extension of Time for 1 month and a check for $110.00. It is believed that no other fees are due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

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Date

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